Original articles

Paraneoplastic limbic encephalitis: Diagnostic relevance of CSF analysis and total body PET scanning

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Abstract

We report two cases of paraneoplastic limbic encephalitis (PLE) that differed in their clinical patterns, the underlying tumours, and the associated paraneoplastic antibodies. The first patient was a young adult male, with anti-MA-2 antibodies and testicular tumour. The clinical picture was restricted to limbic involvement. The second patient was a 56-year-old, female heavy smoker, with seizures and depression, but also vertigo and diplopia. A low level of serum anti-Hu antibodies led to the detection of a small cell lung carcinoma by total body PET-scanning. In both cases, intrathecal synthesis of CSF oligoclonal IgG bands and of the corresponding paraneoplastic antibodies was demonstrated.

Key words: Limbic encephalitis; paraneoplastic antibodies; intrathecal immunity; PET-scan.

Introduction

In 1968, Corsellis et al. first described paraneoplastic limbic encephalitis (PLE) as a clinicopathological entity (Corsellis et al., 1968). The diagnosis of this condition is often difficult because similar symptoms (seizures, memory problems, irritability, depression, confusion, and dementia) can be caused by many other diseases, including brain metastases, toxic and metabolic encephalopathies, herpes simplex encephalitis, and Hashimoto’s encephalitis (Shaw et al., 1991; Bohnen et al., 1997). In addition, neurological symptoms frequently precede detection of any tumour, and involvement of areas of the nervous system distant from the limbic system, particularly the brainstem and the cerebellum, is present in 60% of patients with PLE (Gutelkin et al., 2000).

The detection of anti-neuronal paraneoplastic antibodies (type 1 anti-neuronal nuclear antibody or ANNA-1, also called anti-Hu; anti-Ma2 antibody; anti CV2/CRMP5 antibody; anti-amphiphysin antibody), the presence of an immune reaction in the cerebrospinal fluid (CSF), suggestive MRI abnormalities in the mesial temporal lobes, and use of total body PET scanning (Na et al., 2001; Antoine et al., 2000) have become powerful tools for the accurate diagnosis of PLE and for detection of underlying neoplasms.

We describe two patients with PLE, a 28-year-old male with a mixed testicular tumour and anti-Ma2 antibodies, and a 56-year-old female with small cell lung carcinoma (SCLC) and intrathecal synthesis of anti-Hu antibodies, and stress the diagnostic problems raised by these two cases.

Case reports

PATIENT 1

M.B., born in 1959, a high-school student in agronomy, was first hospitalised in July 1987, in a regional hospital in Belgium, for asthenia and slight hyperthermia (37.4°C). He also complained of gustatory and olfactory changes, olfactory hallucinations, and an impression of “déjà vu”.

The patient was well nourished and general and neurological examinations were normal. The white blood cell (WBC) count was slightly increased (10,600/µL) with neutrophilia. All serological studies were normal, except for a slightly increased titre for Borrelia burgdorferi antibodies (1/256 by an immunofluorescence test). The brain CT scan was normal. The CSF contained 16 mononuclear cells/µL with a normal protein and glucose content. The patient was treated with tetracycline for suspected Lyme disease.

Three days after discharge, he had a tonic-clonic seizure and was re-hospitalised. The CSF contained 9 WBC/µL but was otherwise normal and the electroencephalogram (EEG) showed diffuse slowing in bi-temporal areas without spikes. Two short periods of confusion states were reported after the tonic seizure. Treatment with valproic acid was started.

Two months later, the patient was hospitalised in our Department of Neurology for further investigations. He complained of tiredness, anxiety, memory loss concerning recent events, and persistence of gustatory and olfactory changes. Neurological
examination was normal except for cognitive functions; the patient was slightly disoriented in space and time and displayed severe short-term memory loss. The EEG showed focal abnormalities in the left temporal area with epileptic spikes. During hypopnoea, a focal epileptic discharge was noted in the right temporal area associated with malaise and paresthesia of the feet. A 24 h EEG revealed diurnal hypersomnia and repetitive epileptic discharges in the left temporal area. The brain CT scan remained normal but magnetic resonance imaging (MRI) displayed areas with high signal intensity in both temporal areas on T2 weighted images. Blood analysis revealed no inflammatory signs; infectious and auto-immune serology were negative or within normal ranges, including the anti-Borrelia antibody titre. The CSF contained 15 cells/µL, mostly lymphocytes (70%), normal protein and glucose levels, and numerous IgG oligoclonal bands not present in the corresponding serum. These bands did not display antibody activity against Borrelia burgdorferi or herpes simplex virus (HSV) on antigen-driven immunoblots (Dépré et al., 1988; Monteyne et al., 1997). However, in the presence of such a chronic, and mainly temporal, encephalitis, the patient was treated with intravenous acyclovir (30 mg/Kg/day for 10 days) and with carbamazepine (600 mg/day) and diphenylhydantoin (300 mg/day).

Six weeks later, the MRI showed only a lesion near the right temporal horn. The CSF contained a normal cell count but oligoclonal IgG bands were still present. The memory deficit was unchanged.

In January 1988, while staying in Paris, the patient presented acutely with malignant arterial hypertension with retinopathy due to obstructive renal insufficiency. A left testicular tumour was discovered with voluminous adenopathies and bilateral obstruction of both ureters. A left orchidectomy was performed with ureteral drainage, on 5 January 1988 (Hôpital Cochin, Paris, Prof. Steg). Histological examination revealed a mixed tumour of 2.5/2.0/0.5 cm characterised by the presence of a germ-cell seminoma and a small mature teratoma of a few mm. Chemotherapy was started soon after and was complicated by pneumonia that was treated with antibiotics. After a second course of treatment in February 1988, the patient developed a severe pneumonia and positive haemocultures for Candida albicans. He died from complications of chemotherapy on March 23, 1988. Autopsy revealed a voluminous retroperitoneal tumour that was completely necrotic. Fibrous lesions were observed in both lungs, but no metastases. The brain was not studied.

**Patient 2**

A 56-year-old woman had a first generalised seizure followed by a transient confusional state in September 2000. Since then, her appetite had been bad and her mood, anxious and depressive. The patient believed her change of character was due to family problems. In March 2001, she complained of loss of balance, instability, and vertigo. Because of horizontal diplopia and a second tonic-clonic seizure, she was admitted to our Department of Neurology on April 15, 2001. Valproate treatment was started (1000 mg/day) and she had no further seizures. The patient also had a history of hypothyroidism, treated with thyroxine 50 mg/day. She had been a heavy smoker for twenty years (one to two packs a day).

Examination revealed horizontal diplopia when looking towards the right, with dysconjugated eye movements towards the right, and a limitation of the mobility of the left eye to the left without nystagmus. The vertigo appeared when the patient sat or stood up, and was accompanied by multi-directional instability. Subjectively, the patient described decreased sensation on the outside of the left upper arm and the front of the left thigh; she also described a loss of taste. The neurological examination was otherwise normal. Detailed neuropsychological testing was normal without detectable memory loss.

Thyroid stimulating hormone (TSH) was increased at 8.80 µU/mL (normal range : 0.2 to 3.5). Free T4 and T3 levels were normal. The anti-thyroid peroxidase (TPO) antibody titre was very high, at 22,100 U/ml (normal ≤100), but anti-thyroglobulin antibodies were negative. Echography and scintigraphy of the thyroid gland were normal and a diagnosis of Hashimoto’s thyroiditis was made. Serologic tests for neurotropic viruses (HSV, varicella zoster virus, cytomegalovirus, Epstein-Barr virus) were negative. Tumour markers were not increased (CA 15.3, NSE, CEA, CA 19-9). CSF examination showed a slightly elevated protein level (62 mg/dL; N < 55), 5 cells/µL, and CSF-specific oligoclonal IgG bands. CSF PCR for HSV 1 and 2 was negative. A second CSF sample collected six months later showed similar results.

A brain MRI (Fig. 1) showed increased T2 and FLAIR signal in the right temporal area. EEG and 24-hour EEG showed diffuse slowing (7.5 to 8 c/s) with a slight increase in theta and delta waves, without epileptic activity. Electromyography did not reveal signs of polyneuropathy and repetitive stimulation did not show incremental effects. Total body PET (18FDG) scan (Fig. 2) showed focal hypermetabolism in the right hippocampus and in the posterior part of the right lung hilum. An EEG performed on the same day did not show epileptic discharges. A lung tumour was confirmed by CT-scan, and surgical biopsy enabled us to identify a SCLC.

The first tentative diagnosis was Hashimoto’s encephalitis and the patient received intravenous methylprednisolone, 1 g/day for five days, followed
by oral treatment at decreasing dosage. However, the neurological condition of the patient did not improve and a diagnosis of paraneoplastic encephalitis including limbic and brainstem dysfunction was supported by the finding of the SCLC. The tumour was treated by surgery and appropriate chemotherapy (3 courses of Cisplatine-Vincristine-Epirubicine, CVE). This treatment was followed by a partial pulmonary response. Four months later, a new total body PET scan and a CT-scan showed a reduction in the size of the tumour. However, the ophthalmoplegia had worsened with bilateral limitation of eye movements (left > right) and diplopia in the downward gaze. There was hypoesthesia in the left second branch of the trigeminal nerve. The increased signal in the right temporal area on MRI had disappeared. CSF examination showed 2 cells/µL, persistence of oligoclonal IgG bands, and no malignant cells. At the end of six CVE treatments, six months after the diagnosis, the pulmonary tumour had apparently totally disappeared. Treatment was completed with thoracic radiotherapy. However, neurological signs and symptoms persisted unchanged. The patient was then treated with seven plasma exchanges followed by intravenous immunoglobulin, 0.4 g/Kg/day for five days. No significant neurological improvement was noted.

Ten months after the diagnosis, a sudden worsening of instability occurred, accompanied by slight confusion. A new MRI showed a cerebral metastasis (3 to 4 cm), located in the right frontal lobe. The patient died a few weeks later. Autopsy was not performed.

Anti-neuronal antibodies

Anti-neuronal nuclear antibody (ANNA-1, also called “anti-Hu”) was detected in our laboratory by Western blots. Antigens were extracts of neuronal nuclei from human brains obtained at necropsy of neurologically normal individuals (Pieret et al., 1996).

Sera and CSF from Patient 1 were negative for anti-Hu antibodies, but displayed a specific immunoreactivity against a 40 kd protein. At the same IgG concentration, CSF reactivity was higher than that observed in the serum (Fig. 3). Several years later, these samples were analysed in the laboratory of Prof. J.B. Posner (Memorial Sloan-Kettering Cancer Center, New-York) and were positive for a 40-kd neuronal protein called Ma-2 protein (patient 5 in the paper of Voltz et al., 1999). MA-2 is selectively expressed by normal brain tissue and by testicular tumours associated with PLE.

For patient 2, an initial search for anti-Hu antibodies was negative in the serum at the usual dilution of 1/100. Similar negative results were observed in the laboratory of Dr. Graus (Barcelona) on Western Blots from human neuronal nuclei or rat brain homogenates. However, a weak reactivity compatible with a low titre of anti-Hu antibodies was detected on immunoblots of the HuD protein fusion. This is expected in 16% of patients with...
SCLC without paraneoplastic disorders (Dalmau et al., 1999). By a micro-technique of Western blotting, we finally succeeded in detecting a clear anti-Hu reactivity in the CSF at a dilution of 1/2, similar to that observed in the serum at a dilution of 1/50, although CSF IgG levels were 4 to 7 times lower (Fig. 4). This finding indicated an intrathecal synthesis of anti-Hu antibodies, in relation to the presence of CSF-specific oligoclonal IgG. The presence of anti-Hu antibody in serum and CSF was also confirmed by Dr. Dalmau (University of Arkansas, Little Rock), who excluded a reactivity against Ma1 and Ma2 antigens. In addition, ANNA type I was present at a titre of 1/3840 in the serum, and at a titre of 1/256 in the CSF by immunofluorescence in the laboratory of Dr. V. Lennon (Mayo Clinics, Rochester). Results were negative for amphiphysin I antibodies, Purkinje cell cytoplasmic antibodies, calcium channel N and P/Q type antibodies, acetylcholine receptors and striational antibodies. In addition, anti-CV2/CRMP5 antibodies were also absent (Prof. J. Honnorat, Lyon).

We, therefore, concluded that there was a low serum titre of anti-Hu antibodies in Patient 2 associated with an intrathecal synthesis of these antibodies, indicating an auto-immune mediated PLE.

Discussion

We report two patients with suspected PLE. Notwithstanding the absence of neuropathological confirmation, we believe that these two patients met the diagnostic criteria proposed by Gutelkin et al. (2000) : (i) a clinical picture of short-term memory loss, seizures, or psychiatric symptoms suggesting involvement of the limbic system; (ii) an interval of < 4 years between the onset of neurological symptoms and the cancer diagnosis; (iii) exclusion of other cancer-related complications (metastasis, infection, metabolic and nutritional deficits, cerebrovascular disorder or side-effects of therapy) that may cause symptoms of limbic dysfunction; and (iv) at least one of the following : CSF with inflammatory changes (pleocytosis,
oligoclonal IgG bands) ; MRI showing unilateral or bilateral temporal lobe abnormalities ; and EEG showing slow- or sharp-wave activity in one or both temporal lobes.

Our first patient was initially considered to have herpes simplex encephalitis (HSE) and received treatment with acyclovir without neurological improvement. Onset of HSE is generally acute, and the course of the disease is not as protracted as observed in our case. PCR for HSV genomes is currently the best diagnostic method (Cinque et al., 1996), and a negative result at the first CSF sampling is rarely observed (< 5%). In addition, the CSF-specific oligoclonal IgG bands observed in this case did not display an antibody activity against herpes simplex antigens on antigen-driven immunoblots (Monteyne et al., 1997a ; 1997b). The testicular tumour was discovered at a later stage, and anti-Ma2 antibodies were detected retrospectively (patient 5 in Voltz et al., 1999). Anti-Ma2 antibodies define a subset of PLE patients who are young adult males with testicular tumours.

Our second patient presented with an isolated tonic-clonic seizure, mood disorders and then loss of balance and diplopia. She also suffered from a mild hypothyroidism with replacement low-dose thyroxine, and had auto-antibodies specific to autoimmune thyroiditis. Hashimoto’s encephalopathy may present as a limbic encephalitis with amnestic syndrome, seizures, and bilateral mesial temporal lobe involvement on MRI scans (McCabe et al., 2000). The CSF very frequently contains specific oligoclonal IgG bands. All these characteristics mimic PLE. However, Hashimoto’s encephalopathy responds fairly well to treatment with corticosteroids, whereas our patient did not (Shaw et al., 1991). Low levels of anti-Hu antibodies were detected in the serum of the patient, and at higher concentration in the CSF when both fluids were tested simultaneously on immunoblots. Gultekin et al. (2000) also reported that two patients out of 50 with PLE had barely detectable serum anti-paraneoplastic antibodies, while the CSF titres were several orders of magnitude higher. Intrathecal synthesis of anti-Hu antibodies was reported in 14 of 16 patients with paraneoplastic encephalomyelitis, but in only one of 14 with paraneoplastic subacute sensory neuronopathy (Vega et al., 1994). This
intrathecal synthesis is thus linked to the involvement of the central nervous system and must be looked for in cases with low serum antibody titres but clinical suspicion of PLE. Indeed, low serum levels of anti-Hu antibodies could be observed in up to 16% of patients with SCLC but without paraneoplastic disorders (Dalmau et al., 1992). A 18FDG-PET scan revealed an area of hypermetabolism in the right mesial temporal lobe of our second patient, with no clinical signs of partial complex seizures. A scalp EEG performed on the same day as the PET scanning did not show epileptic activity. However, epilepsia partialis continua has already been described as a manifestation of anti-Hu associated paraneoplastic encephalomyelitis (Shavit et al., 1999). Only three other reports have described hypermetabolic foci in the mesial temporal lobe of patients with limbic encephalitis (Provenzale et al., 1998; Fakhoury et al., 1999; Na et al., 2001). Another explanation could be glucose hypermetabolism due to an inflammatory process. The MRI scans excluded a metastasis and a disruption of the blood-brain barrier because of the hyperintense signal observed in the right temporal lobe was not enhanced by intravenous gadolinium-DTPA injection. Such signals are non-specific and related to vasogenic oedema, cytotoxic oedema or both. They are also present in Hashimoto’s encephalopathy where a vasculitic process is suspected (Nolte et al., 2000). The same FDG-PET scan revealed an occult tumour in the mediastinum that was demonstrated to be a SCLC on biopsy. This technique may show abnormal uptake in the mediastinum in anti-Hu positive patients with negative chest radiography, chest computed tomography and bronchofibroscopy (Antoine et al., 2000). False positives and false negatives do occur, but at a sufficiently low frequency to justify the clinical usefulness of this technique (Rees et al., 2001).

In conclusion, these two cases of PLE underline the importance of the detection of anti-paraneoplastic antibodies, and of their intrathecal synthesis linked to the presence of oligoclonal IgG bands. MRI abnormalities in the mesial temporal lobes may be related to hypermetabolic foci detectable by a 18FDG-PET scan. The latter has a high sensitivity for the detection of occult tumours, and, if negative, should be repeated every six months (Antoine et al., 2000). As the ability of the PET scan to detect a subclinical primary testicular tumour is not yet established, the follow-up should include periodic ultrasound examination of the scrotum in young males with clinically suspected PLE. Some anti-Hu positive patients may develop a cancer up to 8 years after the onset of the neurological disorder (Luchinetti et al., 1998). It should, however, be kept in mind that many PLE patients remain seronegative for the so far known paraneoplastic antibodies (up to 40% in the series of Gultekin et al. (2000)). A negative test, therefore, does not rule out the possibility of a paraneoplastic disorder and the presence of an underlying neoplasm (Alamowitch et al., 1997; Dropcho, 1998).

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REFERENCES


Bohnen N. I. L. J., Parnel K. J., Harper C. M. Reversible MRI findings in a patient with


